REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 39, 41, 48, 50, 51, 64, 66 and 67 have been canceled without prejudice or disclaimer of the subject matter recited therein. Further, claims 38, 40, 47, 49, 52, 53, 55, 63, 65, 68, 69, 71 and 74 have been amended to further clarify Applicants' invention. Support for the amended claims can be found throughout the specification. Accordingly, no new matter has been added.

I. Rejections under 35 U.S.C. § 112, first paragraph

Claim 38 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner has stated that because the specification does not specifically exclude the E7 and L2 combination of polypeptides, the negative limitation in claim 38 is new matter. Applicants respectfully traverse this rejection.

Applicants submit that in *In re Wright*, 866 F.2d 422 (Fed. Cir. 1989), the Federal Circuit found that exclusionary language (e.g., a provisio) was adequately described in the specification when the specification was read in light of the prior art. It was clear in *In re*

Wright that by teaching certain characteristics or features of the claimed invention, the specification implies that other characteristics or features are undesirable and should be excluded. Therefore, the court concluded that the exclusionary phrase was adequately described. Further, the Federal Circuit in *In re Wright* stated that the claimed subject matter need not be described "in haec verba." Based on *In re Wright*, applicants consider that the use of the exclusionary phrase in claim 38 of the present application is proper in light of the particular characteristics of the described below.

The claims of the present application are drawn to pharmaceutical compositions for the treatment of HPV infections and other serious pathologies such as cancer of the neck and of the uterus. Further, the goal of the present invention is to establish lasting immunity against HPV and to limit the propagation of HPV infections. These features of the present invention require that HPV antigens, which will be effective prophylactically, be employed in the pharmaceutical compositions. Thus, it is contrary to the goals of the present invention and it would not be practical to use HPV antigens that are known to produce no prophylactic effects.

For example, an L2+E7 containing vaccine is detailed in WO93/00436 (Jarrett et al.) and WO94/23037 (Campo et al.) cited in the International Search Report and in the Information Disclosure Statement annexed to the first Official Action mailed on April 8, 1999. The L2 and E7 polypeptides of BPV-4 are produced by a recombinant route in E. Coli as GST fusion proteins. An antitumoral protection of immunoprophylactic type is observed in calves vaccinated with the mixture of purified GST-fused L2 + E7

polypeptides before the viral challenge (Figure 4 and Example 2 of WO 93/00436; Experiment #4 of Table 2, page 21 and Figure 3B of WO 94/23037). When comparing Figures 3 and 4 of WO 93/00436 and Figures 3B and 3C of WO 94/23037, one concludes that vaccination with either L2 or L2 +E7 results in the same prophylactic protective effect (in other words E7 is inefficient in this context). Moreover, in spite of the presence of E7 early polypeptide, the L2+E7 vaccine does not confer any protection against tumors pre-existing before the vaccination (therapeutic effect), as indicated in WO 93/00436 (page 15, last paragraph) and in WO 94/23037 (page 21, lines 22-25).

Further, it is interesting to note that recent data report the inefficiency of this L2+E7 formulation (Cantab Pharmaceutical's TH-GW human papillomavirus vaccine comprising a mixture of L2 and E7 polypeptides of HPV-6 produced in E. coli) (submitted with the previous response dated January 8, 2001) and indicate that human clinical assays using the Cantab vaccine have been stopped due to its failure to demonstrate any therapeutic improvement over a placebo (see *Antiviral Agents Bulletin*, Vol. 13, enclosed herewith). This data as well as the publications discussed above establish that the L2/E7 combination is ineffective and undesirable and teach away from the claimed invention. Thus, in accordance with *In re Wright* and in view of the discussion above, the specification implies that the L2 and E7 combination is undesirable and should be excluded.

In light of the foregoing, the specification adequately describes the exclusionary language, particularly when the specification is read in light of contemporary knowledge in the field. Hence, the proviso phrase which was included in claim 38 by way of the

Amendment and Reply filed on January 8, 2001 is not new matter. Accordingly, the Examiner is respectfully requested to withdraw the rejection of claim 38 under 35 U.S.C. § 112, first paragraph.

Claims 39-41, 48-50, 55-57, 64-66, 71, and 72 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a nononcogenic variant of E6 having amino acids 111-115 deleted and a nononcogenic variant of E7 having amino acids 21-26 deleted, allegedly does not reasonably provide enablement for any polypeptide variant that has 75% sequence homology with E6 and E7. Applicants respectfully traverse this rejection.

However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have canceled claims 39, 41, 48, 50, 64 and 66 and amended claims 55 and 71 to recite a nononcogenic variant of E6 having amino acids 111-115 deleted and a nononcogenic variant of E7 having amino acids 21-26 deleted. Support for these amendments can be found at least on page 18, lines 32-35, and page 19, lines 3-8, of the specification.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 39-41, 48-50, 55-57, 64-66, 71, and 72 under 35 U.S.C. § 112, first paragraph.

II. Rejections under 35 U.S.C. §§ 102(a)/103(a)

Claims 38-50, 58-60, 62-66, 74-76 and 78 have been rejected under 35 U.S.C.

§ 102(a) as allegedly being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over Stanely et al. (WO 96/29091). Applicants respectfully traverse this rejection.

Stanley et al. discloses that IL-12 is present in 100% of regressing HPV-induced tumors surveyed in the course of clinical studies, unlike many other cytokines also surveyed (see page 3 lines 11-14). Given the association between the presence of IL- 12 in lesions resulting from HPV infection and regression of these lesions, Stanley et al. proposes to use IL- 12 as a therapeutic agent in the treatment of papillomavirus-associated lesions. In addition, the IL-12 treatment can comprise in combination a papillomavirus antigen for use as a vaccine. As indicated on page 4, lines 33-38 of Stanley et al., the combination composition can comprise at least one papillomavirus polypeptide or a substantial part thereof of at least one of proteins E1, E2, E4, E5, E6, E7, LI and/or L2 of HPV 6, 11, 16 and/or 18. In other words, Stanley et al. either considers using a single polypeptide selected from any of the papillomavirus antigens or any possible combination (i.e. E1+E2, E1+E4, E1+E5, E1+E6, E1+E7, E1+ L1, E1+L2, E2+E4, E2+E5, E2+E6, E2+E7, E2+L1, E2+L2, etc. or E1+E2+E3, E1+E2+E4, etc.) which represents more than 80 possible combinations

Stanley et al. does not consider injecting papilloma polypeptides in the absence of IL-12 to treat or prevent papillomavirus-induced lesions or tumors. Therefore, claim 38 and, by way of consequence, its dependent claims 40, 42-46 are novel in view of Stanley et al. With respect to claims 47 and 63 and their respective dependent claims, which specify

an immunostimulatory molecule-containing composition, Applicants have amended these claims to recite specific immunostimulatory polypeptides selected from the group consisting of IL-2, IL-7, B7.1 and B7.2. Support for such amendments can be found in original claims 51 and 67, respectively.

Applicants draw the Examiner's attention on the fact that Stanley et al. recognized that non IL- 12 cytokines do not play any role in HPV-induced tumors regression as indicated page 3, lines 13-14 of WO 96/29091. In particular, the experimental data clearly establish that IL-2 expression is quite different from IL-12 expression in the different categories of cervical biopsies analysed in this study. Indeed, in marked contrast to IL-12, IL-2 transcripts are detected in normal cervix (see Table E of Stanley et al.), as well as in some of the non-regressing lesions (5/8 in Table C, 2/7 in Table B of Stanley et al.). Relying on these data, Stanley et al. does not provide sufficient guidance to suggest a reasonable expectation of success when employing immunostimulatory polypeptides other than IL-12 (e.g., IL-2, IL-7, B7.1 and B7.2) to treat HPV-induced lesions. Therefore, one of ordinary skill in the art would not be motivated to associate such immunostimulatory molecules with HPV polypeptides to provide lasting immunity and limit the occurrence.

However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants submit that the subject application claims priority to French Application No. 96 09584 under 35 U.S.C. § 119, which was received by the U.S. Patent and Trademark Office from the International Bureau on March 30, 1998 and acknowledged as received by the Examiner in the Official Action dated August 4,

1999. The French priority application has a filing date of July 30, 1996 which antedates Stanley et al.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 38-50, 58-60, 62-66, 74-76 and 78 under 35 U.S.C. §§ 102(a) and 103(a).

III. Rejections under 35 U.S.C. § 103(a)

Claims 40, 49 and 64 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stanley et al. Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986).

Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d

1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Stanley et al. teaches that IL-12 expression is active in HPV-induced lesions which are beginning to regress and therefore propose to treat HPV-infected patients with IL-12 to facilitate regression of their lesions. In order to enhance regression, Stanley et al. proposes to combine IL-12 treatment with at least one papillomavirus antigen or antigenic fragment thereof to boost immunity against HPV. The Examiner asserts that the HPV polypeptides and antigenic fragments taught by Stanley et al. are non oncogenic variants because any peptide that would not treat papillomavirus infections and would cause antigenic lesions would be excluded from the teaching of Stanley et al. This statement appears to be the Examiner's own interpretation and goes beyond the accurate teaching of WO 96/29091. Stanley et al. does not mention, suggest or teach nononcogenic variants of papillomavirus antigens. Further, the Examiner has indicated that the reference of Stanley et al. to substantial portion of HPV polypeptides anticipates the instant application in claiming a sequence homology greater than 75% with the papillomavirus proteins. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have canceled claims 39, 41, 48, 50, 64 and 66, which recited at least 75% homologous HPV sequence. Moreover Stanley et al. does not teach a prophylactic vaccine to treat papillomavirus infections with a composition that includes HPV polypeptides and an immunostimulatory polypeptide such as those specified.

In addition, Applicant have outlined above the reasons as to why Stanley et al. neither anticipates or renders obvious the claimed invention. Further, Applicants remind the Examiner that the subject application claims priority to French Application No. 96 09584 under 35 U.S.C. § 119, which was received by the U.S. Patent and Trademark Office from the International Bureau on March 30, 1998 and acknowledged as received by the Examiner in the Official Action dated August 4, 1999. The French priority application has a filing date of July 30, 1996 which antedates Stanley et al.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 40, 49 and 64 under 35 U.S.C. § 103(a).

Claims 38-55 and 58-78 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Galloway, Hines et al., and Gajewski. Applicants respectfully traverse this rejection.

Galloway et al. is a review of human papillomavirus vaccines. This document teaches that it should be feasible to develop prophylactic vaccines to prevent HPV infections using the L1 and L2 capsid proteins or therapeutic vaccines to modulate the development or reoccurrence of disease based on the E6 and E7 oncoproteins or other viral proteins. Galloway et al. discusses preclinical studies that have been performed with either late papillomavirus polypeptide (see page 190 second column of Galloway et al.) or early papillomavirus polypeptide (see page 191 from the second sentence to the end of the first paragraph of the first column of Galloway et al.).

Applicants draw the Examiner's attention to the fact that all prophylactic vaccination studies were performed with late papillomavirus polypeptides recombinantly produced as fusion proteins. For example, Galloway et al. describes i) calves vaccinated with BPV 2 L1 or L2 fusion proteins that developed fibromas or fibropapilloma, respectively, which regressed rapidly postchallenge in comparison with unvaccinated calves; ii) similar results reported for another cutaneous BPV, BPV-1, and an L2 fusion protein from a mucosal virus (BPV-4) protected against challenge by BPV-4 via the palate; and iii) more recent studies showing that either L1 or L2 CRPV fusion proteins could confer immunity.

Therapeutic vaccinations include *in situ* production of papilloma early antigens produced from tumoral cell lines or recombinant viruses that have been injected into the host (Mice inoculated with fibroblasts expressing HPV 16 E6 or E7 could reject challenge by a melanoma cell line expressing the HPV oncogenes. Vaccinia virus recombinants expressing the BPV E5, E6 or E7 genes could retard the development of tumors resulting from challenge with a BPV-transformed cell line in syngenic rats).

Galloway et al. further discloses at page 191 second column that it is unclear "whether therapeutic vaccines should be based on early or late antigens or combination of these." The only combination which is disclosed in this document relies on an L2-E7 fusion protein (see paragraph bridging page 190 and 191). As discussed in our response to the previous Official Action, the L2+E7 containing vaccine is described in WO 93/00436 (Jarrett et al.) and WO 94/23037 (Campo et al.) cited in the international search report and in the information disclosure statement annexed to the first Official Action mailed on April

8, 1999. The L2 and E7 polypeptides of BPV-4 are produced by recombinant route in E. coli as GST fusion proteins. An antitumoral protection of immunoprophylactic type is observed in calves vaccinated with the mixture of purified GST-fused L2 + E7 polypeptides before the viral challenge (Figure 4 and Example 2 of WO 93/00436 ; Experiment # 4 of Table 2, p21 and Figure 3B of WO 94/23037). When comparing Figures 3 et 4 of WO 93/00436 and Figures 3B et 3C of WO 94/23037, one concludes that vaccination with either L2 or L2+E7 results in the same prophylactic protective effect (i.e., E7 is inefficient in this context). Moreover, in spite of the presence of E7 early polypeptide, the L2+E7 vaccine does not confer any protection against tumors preexisting before the vaccination (therapeutic effect), as indicated in WO 93/00436 (see page 15, last paragraph) and in WO 94/23037 (see page 21, lines 22-25).

As already mentioned to the Examiner, the human clinical assays using Cantab's TH-GW vaccine (based on an L2-E7 fusion protein) were stopped due to its failure to demonstrate any therapeutic improvement over a placebo (see Antiviral Agents Bulletin Vol 13, already provided to the Examiner).

In summary, Galloway et al. teaches a composition comprising:

- (an) early papillomavirus polypeptide(s) to treat HPV infections
- (a) late papillomavirus polypeptide(s) expressed as a fusion protein to prevent HPV infections, and
- a E7+L2 fusion protein.

As a result, one skilled in the art would not be motivated to modify the composition of Galloway et al. to arrive at the present invention since it is unclear from the prior art whether other early and late HPV polypeptide combinations could provide effective protection or treatment against HPV-induced diseases. Moreover, Galloway et al. does not teach the action of immunostimulatory polypeptides to enhance the protective effect conferred by the papilloma polypeptides.

Applicants remind the Examiner that the L2+E7 containing composition was specifically disclaimed from the instant invention in response to a previous Official Action. However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 38 to further clarify Applicants' invention. Specifically, claim 38 has been amended to recite that the papilloma polypeptides are expressed recombinantly from independent expression control elements. Support for this amendment can be found in original claims 47 and 63.

Hines et al. relates to recombinant papillomavirus-like particles used as prophylactic subunit vaccines to protect against naturally transmitted HPV infections. Beside this prophylactic aspect, Hines et al. discusses a cellular adoptive therapy protocol which relies on the administration of cytotoxic T lymphocytes. The naive lymphocytes obtained from a host's peripheral blood lymphocytes or a histocompatible donor are then *in vitro* stimulated with IL-2 and an HPV early peptide before being perfused into the cancer patient (see page 862, second column, last paragraph of Hines et al.).

In summary, Hines et al. discloses (1) a pharmaceutical composition intended for the prevention of a papillomavirus infection or tumor which comprises as therapeutic agent virus-like particles made of late L1 and L2 HPV polypeptides and (2) a pharmaceutical composition intended for the treatment of a papillomavirus infection or tumor which comprises as therapeutic agent cytototoxic T lymphocytes *in vitro* stimulated by an HPV early peptide and IL-2 (i.e., a cellular composition).

Thus, Hines et al teaches to inject into a patient a lymphocyte composition previously *in vitro* activated by the action of IL-2 and an HPV peptide. Contrary to the Examiner's statement, Hines et al. does not teach injecting IL-2 into a patient together with HPV (poly)peptides to enhance the protective effect conferred by the papilloma polypeptides.

Gajewski relates to B7.1-induced stimulation of naive lymphocytes to cytotoxic T lymphocytes (CTLs). To this end, the B7.1 cDNA was transfected into P815 mastocytoma cells. Mouse splenocytes were then stimulated with the transfected cells in the presence of an anti-CD3 antibody. B7.1 transfected tumor cells stimulated proliferation of CD4+ as well as CD8+ T cells. As discussed on page 470 of Gajewski, direct co-stimulation of CD8+ T lymphocytes by expression of B7.1 allows the emergence of CTLs that produce their own IL-2. It is suggested that expression of B7.1 on human tumor cells can render them better able to stimulate CD8+ lymphocytes and that utilization of B7.1-expressing autologous tumor cells may provide a plausible immunization approach for cancer patients.

Thus, Gajewski is not relevant to the instant invention as it is primarily directed towards the use of a cellular composition comprising B7.1 transfected tumor cells to treat a cancer patient. Gajewski does not mention or suggest to inject B7.1 together with a (HPV) polypeptide to provide protection against a viral (HPV) infection.

In conclusion, the references cited by the Examiner, singly or in combination, do not render obvious the claimed invention which is drawn to a composition associating an HPV polypeptide with an immunostimulatory polypeptide because Galloway et al. fails to teach the action of the immunostimulatory polypeptide to enhance the protection conferred by the papilloma polypeptides and this element is not taught by the disclosures of Hines et al. and Gajewski which relate to *in vitro* stimulated cellular compositions.

Further, with respect to pending claims reciting a composition combining early and late HPV polypeptides, the references cited by the Examiner do not render the instant claims obvious since Galloway et al. teaches the use of fusion HPV proteins.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 38-55 and 58-78 under 35 U.S.C. § 103(a).

Claims 56 and 57 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Galloway, Hines et al. and Gajewski as applied to claims 38-55 and 58-78 above, and further in view of Munger et al. and Crook et al. Applicants respectfully traverse this rejection.

The discussion regarding Galloway, Hines et al., and Gajewski above is incorporated herein by reference. With regard to Munger et al. and Crook et al., page 5,

lines 2-6, of the present application states that Munger et al. and Crook et al. disclose the nononcogenic variants of the E6 and E7 HPV polypeptides.

As already discussed above, the combination of Galloway, Hines et al., and Gajewski do not render the claimed invention obvious. Munger et al. and Crook et al. in combination with the with Galloway, Hines et al., and Gajewski also do not render the claimed invention obvious.

As the specific combinations claimed in the pending independent claims are patentable, the patentability also applies to the dependent claims reciting a composition comprising the nononcogenic variants of the E6 and E7 HPV polypeptides.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 56 and 57 under 35 U.S.C. § 103(a).

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Mercedes K. Meyer, Reg. No. 44,939

By: MERCEDES K. MEYER
for Teresa Stanek Rea
Registration No. 30,427

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: September 5, 2001

Attachment to Amendment dated September 5, 2001
Marked-up Claims

38. (Amended) A pharmaceutical composition intended for the treatment or prevention of a papillomavirus infection or tumor, which comprises as therapeutic agents at least one polypeptide from the early region of a human papillomavirus and at least one polypeptide from the late region of a human papillomavirus with the exception of the specific combination of a polypeptide from the E7 early region of a human papillomavirus and a polypeptide from the L2 late region of a human papillomavirus and wherein said polypeptide from the early region of a human papillomavirus and said polypeptide from the late region of a human papillomavirus are expressed recombinantly from independent expression control elements.

40. (Amended) The pharmaceutical composition according to claim [39] 38, wherein the polypeptide from the early region of a papillomavirus is a nononcogenic variant of the E6 and/or E7 protein of a papillomavirus.

47. (Amended) A pharmaceutical composition intended for the treatment or prevention of a papillomavirus infection or tumor, which comprises as therapeutic agents at least one polypeptide from the early region of a papillomavirus and at least one polypeptide from the late region of a papillomavirus and at least one polypeptide having an immunostimulatory activity, wherein said polypeptide from the early region of a

papillomavirus and said polypeptide from the late region of a papillomavirus and said polypeptide having an immunostimulatory activity are expressed recombinantly from independent expression control elements and wherein said polypeptide having immunostimulatory activity is selected from the group consisting of interleukin-2, interleukin-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2.

49. (Amended) The pharmaceutical composition according to claim [48] 47, wherein the polypeptide from the early region of a papillomavirus is a nononcogenic variant of the E6 and/or E7 protein of a papillomavirus.

52. (Amended) The pharmaceutical composition according to claim [51] 47, wherein the polypeptide having an immunostimulatory activity is interleukin-2.

53. (Amended) The pharmaceutical composition according to claim [51] 47, wherein the polypeptide having an immunostimulatory activity is the co-adhesion molecule B7.1.

55. (Amended) The pharmaceutical composition of claim 47, wherein said composition comprises:

(a) a nononcogenic variant of an E6 protein of a human papillomavirus, wherein said nononcogenic variant is a variant of the native E6 protein [mutated at

the level of residues involved in the process of transformation of an infected cell] having amino acids 111-115 deleted as compared to the native E6 protein,

(b) a nononcogenic variant of an E7 protein of a human papillomavirus, wherein said nononcogenic variant is a variant of the native E7 protein [mutated at the level of residues involved in the process of transformation of an infected cell] having amino acids 21-26 deleted as compared to the native E7 protein,

(c) a polypeptide from the L1 region of a human papillomavirus,

(d) a polypeptide from the L2 region of a human papillomavirus, and

(e) interleukin-2.

63. (Amended) A pharmaceutical composition intended for the treatment or prevention of a papillomavirus infection or tumor, which comprises as therapeutic agents at least one polypeptide from the early region or late region of a papillomavirus and at least one polypeptide having an immunostimulatory activity, wherein said polypeptide from the early region of a papillomavirus and said polypeptide from the late region of a papillomavirus and said polypeptide having an immunostimulatory activity are expressed recombinantly from independent expression control elements and wherein said polypeptide having an immunostimulatory activity is selected from the group consisting of interleukin-1, interleukin-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2.

65. (Amended) The pharmaceutical composition according to claim [64] 63, wherein the polypeptide from the early region of a papillomavirus is a nononcogenic variant of the E6 and/or E7 protein of a papillomavirus.

68. (Amended) The pharmaceutical composition according to claim [67] 63, wherein the polypeptide having an immunostimulatory activity is interleukin-2.

69. (Amended) The pharmaceutical composition according to claim [67] 63, wherein the polypeptide having an immunostimulatory activity is the co-adhesion molecule B7.1.

71. (Amended) The pharmaceutical composition according to claim 63, wherein said composition comprises:

(a) a nononcogenic variant of an E6 region of a human papillomavirus, wherein said nononcogenic variant is a variant of the native E6 protein [mutated at the level of residues involved in the process of transformation of an infected cell] having amino acids 111-115 deleted as compared to the native E6 protein; and

(b) a nononcogenic variant of an E7 region of a human papillomavirus, wherein said nononcogenic variant is a variant of the native E7 protein [mutated at the level of residues involved in the process of transformation of an infected

cell] having amino acids 21-26 deleted as compared to the native E7 protein; and

(c) interleukin 2.

74. (Amended) The pharmaceutical composition of claim 63, wherein the papillomavirus is selected from the group consisting of HPV-16, HPV-18, HPV-31, HPV-33 and HPV-45 types.